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09/449,077	11/24/1999	Dr. Thomas Hunig	12254/	5838

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/449,077	HUNIG, DR. THOMAS	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *5-12, 16-23 and 25-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 13-15, 24, 41-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 1/14/04, has been entered.
Claim 1 has been amended.
Claims 42-46 have been added.

Claims 1-46 are pending.

Claims 5-12, 16-23 and 25-40 have been withdrawn from consideration.

Claims 1-4, 13-15, 24, 41-42 and newly added claims 43-46 are under consideration in the instant application.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 1/14/04.
The rejections of record can be found in the previous Office Action, mailed 7/14/03.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. New Matter: Claim 43 is rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed:

"without occupancy of an antigen receptor of the human T lymphocytes, and <u>without T cell receptor stimulation</u>"

Applicant's amendment, filed 1/14/04, directs support for new claim 43 to page 1, paragraph 2, line 2 and Example 1, particularly page 7 of the instant specification.

While it is acknowledged that the recitation of "without occupancy of an antigen receptor of the human T lymphocytes," is supported by the specification as filed, the written description of the recitation of the underlined element "and <u>without T cell receptor stimulation</u>" is not readily apparent in the instant specification as filed.

Also, as pointed out below in the rejection under 35 U.S.C. § 112, first paragraph, enablement, it is not readily apparent that the T cells proliferate without T cell receptor stimulation even by direct stimulation with CMY-2-specific / CD28-sepcific antibodies, given that the DMY-2 antibodies were used in the form of unclean culture supernatant in vitro in Example 1 or used in vivo in Example 3 of the instant specification.

The specification as filed does not provide a written description or set forth the metes and bounds of this phrase. The specification does not provide blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as they are currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office action

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above. See MPEP 714.02 and 2163.06

5. Claim 46 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

It is apparent that the CMY-2 antibody produced by the hybridoma cell line DSM ACC 2353 is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the DSM ASC 2353 hybridoma which produces this antibody. See 37 CFR 1.801-1.809.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

5. Again claims 2(b) is object to in that "pursuant" should be spelled "pursuant".

6. Upon reconsideration of applicant's amended claim 1, the previous rejection under 35 U.S.C. § 112, second paragraph, with respect to the recitation of "human-compatible monoclonal antibody" has been withdrawn.

7. Claim 46 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 46 lacks proper antecedent basis from claim 1 because independent claim 1i s drawn to a humanized monoclonal antibody while the monoclonal antibody CMY-2 produced by the hybridoma cell line DSM ACC 2353 appears to be a monoclonal antibody and not a humanized monoclonal antibody.

Applicant is invited to amend claim 46 to indicate the proper relationship between the monoclonal antibody CMY-2 produced by the hybridoma cell line DSM ACC 2353 and the humanized monoclonal antibody recited in claim 1.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

8. Claims 1-4, 13-15, 24, 41-42 and newly added claims 43-45 are rejected under 35 U.S.C. § 102(e) as being anticipated by June et al. (U.S. Patent No. 5,858,358) (see entire document) for the reasons of record.

Applicant's arguments, filed 1/14/04, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant argues that the claimed recitation of "without occupancy of an antigen receptor", including the indication of the present specification that occupancy of the T cell antigen receptor includes binding by an antibody such as anti-CD3 antibody distinguishes the instant claimed antibodies from the prior art teaching of agonistic anti-CD28 antibodies.

However, as page 7, paragraph 5 of the instant specification notes, CD3 is part of the T cell receptor complex and can ensure T cell receptor stimulation. Antibodies that bind CD3 are distinguishable from antibodies that bind the T cell receptor, as it reads on the claimed recitation "without occupancy of an antigen receptor of the human T lymphocytes".

As pointed out previously, it has been noted that Example 3 of the instant specification discloses that "it is not necessary to crosslink them artificially by means of a second antibody. Rather the presence of non-T cell from lymphoid organs, viz. from B lymphocytes and so-called accessory cells, is sufficient to make a direct activation by solubly added CD28-specific monoclonal antibodies possible. This probably happens through the binding of the monoclonal antibodies to so-called Fc receptors of these non-T cells. This resulted is an important precondition of the therapeutic use of directly stimulating CD28-specific monoclonal antibodies, in which an artificial crosslinking with anti-immunoglobulin antibodies in the entire organism is not practicable".

The prior art as well as the disclosed agonistic CD28-specific antibodies can act through direct activation either via crosslinking by secondary antibodies or by binding with Fc receptor expressing cells. The claimed recitation "without being artificially crosslinked with a secondary antibody encompasses alternative methods of crosslinking or binding CD28-specifci antibodies in order for said agonistic antibodies to stimulate T cells.

Given that the prior art agonistic CD28-specific antibodies stimulated T cells via a primary activation signal or the CD3 complex such as anti-CD3 antibody (e.g. see column 5, paragraph 1-3), the prior art CD28-specific antibodies stimulated T cells directly without occupancy of antigen receptor of human T lymphocytes (e.g. T cell receptor).

In contrast to applicant's arguments that the June et al. does not teach humanized antibodies and as pointed out previously, the prior art combinatorial antibodies anticipate the claims, if the claims were intended to recite humanized antibodies, as currently amended and recited.
Thus the prior art agonistic CD28-specific antibodies would have had the inherent properties encompassed by the claimed products.

Applicant's arguments have not been found persuasive.

9. Claims 1-4, 13-15, 24, 41-42 and newly added claims 43-45 are rejected under 35 U.S.C. § 103(a) as being unpatentable over June et al. (U.S. Patent No. 5,858,358) in view of Tacke et al. (Eur. J. Immunol. 27 : 239-247, 1997) and in further view of applicant's acknowledgedment on page 4, lines 1-8 of the specification that production of hybridoma cells, humanization of antibodies and production of monclonal antibodies from humanized hybridoma cells was well known, as also evidence by Bendig et al. (U.S. Patent No. 5,558,864) of the reasons of record.

Applicant's arguments, filed 1/14/04, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments the examiner's rebuttal are essentially the same of record.

Again, applicant argues that the '358 Patent in combination with Tacke et al. do not render the claimed invention obvious, as the antibodies disclosed in the '358 Patent do not cause T cell proliferation upon binding to said CD28 on all classes of said T cells, (e.g. without T cell receptor stimulation; compare claim 1 and 43) and Tacke et al. did provide a reasonable expectation of success that a human anti-CD28 antibodies could be generated having the claimed properties.

As pointed out previously, it has been noted that Example 3 of the instant specification discloses that "it is not necessary to crosslink them artificially by means of a second antibody. Rather the presence of non-T cell from lymphoid organs, viz. from B lymphocytes and so-called accessory cells, is sufficient to make a direct activation by solubly added CD28-specific monoclonal antibodies possible. This probably happens through the binding of the monoclonal antibodies to so-called Fc receptors of these non-T cells. This resulted is an important precondition of the therapeutic use of directly stimulating CD28-specific monoclonal antibodies, in which an artificial crosslinking with anti-immunoglobulin antibodies in the entire organism is not practicable".

The prior art as well as the disclosed agonistic CD28-specific antibodies can act through direct activation either via crosslinking by secondary antibodies or by binding with Fc receptor expressing cells. The claimed recitation "without being artificially crosslinked with a secondary antibody encompasses alternative methods of crosslinking or binding CD28-specifci antibodies in order for said agonistic antibodies to stimulate T cells.

Given that the prior art agonistic CD28-specific antibodies stimulated T cells via a primary activation signal or the CD3 complex such as anti-CD3 antibody (e.g. see column 5, paragraph 1-3), the prior art CD28-specific antibodies stimulated T cells directly without occupancy of antigen receptor of human T lymphocytes (e.g. T cell receptor).

As pointed out previously, applicant's arguments including the numerous citations to the prior art are consistent with the prior art agonistic CD28-specific antibodies that can stimulate T cells in the absence of occupying the T cell receptor, whereby the CD28-specific antibodies stimulate T cells via other primary or activation signals (e.g. PMA or anti-CD3 antibodies).

With respect to the teachings of Tacke et al., it has been noted previously that Tacke et al. teach the production of hybridomas secreting a rat antibody to human CD28 and the characterization of the rat antibody JJ316 (see entire reference including Abstract). Tacke et al. Teach that the rat antibody JJ316 is specific for rat CD28 and can activate proliferation of all T cell subsets without T cell receptor occupancy (see entire document, especially Figure 2 and Section 3.4). Tacke et al. Also teach that the ability of the JJ16 antibody to « directly » stimulate is due to a difference in fine specificity versus other anti-CD28 antibodies that do not directly stimulate; and that antibodies with this fine specificity can be generated by immunizing with CD28 transfected cell lines more readily than by immunizing with T cells with naturally express CD28 (see especially page 245, column 2).

Given the teachings of Tacke e tal. That directly stimulating antibodies can be produced by immunizing with a cell line transfected with human CD28, it would have been obvious to one of ordinary skill in the art at the time the invention was made to screen the antibodies taught by June et al. (or to produce additional antibodies) for those monoclonal antibodies and the hybridomas producing them which are specific for human CD28 and which directly activate human T cells without occupancy of the T cell antigen receptor. One would have been motivated to screen for such antibodies and hybridoma producing them in order to derive antibodies that could be used without anti-CD3 antibodies in the methods of June et al. to expand T cell for human therapy. Given the teachings of Tacke et al. that anit-CD28 antibodies which directly stimulate T cells without occupancy of the T cell receptor are produced using immunization strategies based upon transfected cell lies rather than T cells and the teachings of June et al. that transfected cell lines could be and were used; one of ordinary skill in the art would have had a reasonable expectation that directly stimulating antibodies specific for human CD28 were produced or could be produced using the method of June et al. and could be identified as taught by Tacke et al.

Therefore, the prior art provided proper motivation for screening the antibodies of June et al. to identify these expected properties in order to identify antibodies that could be used without anti-CD3 to expand T cells for human therapy, as taught by June et al. The examiner has also provided a reasonable expectation of successful isolating antibodies having the instantly recited properties because Tacke et al. teach that the instantly recited properties are expected properties of antibodies produced using transfected cells.

As acknowledged by applicant on page 4, lines 1-8 of the instant specification, methods of humanizing antibodies were well known in the art at the time the invention was made, as evidenced by Bendig et al. Bendig et al. also teach that human-compatible antibodies are desirable in order to reduce immunogenicity and improve antibody half-life and efficacy when administered to a human (see entire document, including columns 21-22).

It would have been obvious to the ordinary artisan at the time the invention was made to humanize the monoclonal antibodies specific for human CD28 taught by June et al., including those antibodies which directly activate T cells without occupancy of the T cell antigen receptor. Given the art-recognized methods of humanizing antibodies, as acknowledged by applicant and as evidenced by Bendig et al., the ordinary artisan would have had a reasonable expectation of success. In addition, Bendig et al. teach the ordinary artisan at the time the invention was made was motivated to humanize antibodies in order to produce improved therapeutics.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidence by the references, especially in the absence to the contrary.

Applicant's arguments have not been found persuasive.

10. Claims 1-4, 13-15, 24, 41-42 and newly added claims 43-45 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Siefken et al. (Cell Immunol. 176 : 59-65, 1997) in view of applicant's acknowledgement on page 4, lines 1-8 of the specification that production of hybridoma cells, humanization of antibodies and production of monoclonal antibodies from humanized hybridoma cells was well known, as also evidence by Bendig et al. (U.S. Patent No. 5,558,864) for the reasons of record.

Applicant's arguments, filed 1/14/04, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant notes that it is not understood why the rejection over Siefken et al. has been maintained since Siefken et al. disclose the BW 828 required crosslinking to induce proliferation (e.g. see page 61, Table 2 of Siefken et al.).

Applicant notes that it is not clear why the prior art disclosure of the BWSW 828 antibody required crosslinking to induce proliferation

Siefken et al. Teach the production of hybridoma-produced antibodies to human CD28 and that the BW 828 antibody could activate human T cells without co-engagement of the T cell antigen receptor/CD3 complex (see entire document, especially Materials and Methods and Discussion).

Figure 4 shows that while memory (CD45RO+) cells certainly proliferated more readily, CD45RA+ cells also show some increase in proliferation (compare white boxes of Figure 4). Further, depending upon which subgroup one is considering, there are other T lymphocyte subsets encompassed within those cells that are CD45RO+. For example, one may subset CD45RO+ cells based upon their T cell receptor gene usage, chemokine receptor expression, expression of CD25, etc. The instant claims do not require any particular subgroup and therefore are not at present distinguished from the teachings of Siefken et al.

For the reasons of record and addressed herein, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidence by the references, especially in the absence to the contrary.

Applicant's arguments have not been found persuasive.

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11. No claim allowed.

The specific monoclonal antibody CMU-2 produced by the hybridoma cell line DSM ACC 2353 appears free of the prior art. Further, due to high polymorphism of antibodies, the CMY-2 antibody produced by the hybridoma cell lines DSM ACC 2353 is deemed structurally distinct on the primary amino acid basis and therefore free from the prior art.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
April 9, 2004